Docket No.: 5976-0111PUSI
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Jan MOLLENHAUER et al.

Application No.: 10/590,657

Confirmation No.: 1500

Filed:J\ugust25,2006

Art Unit: 1645

For: USE OF DMBTI FOR CAPTURING SULPHATE AND PHOSPHATE GROUP EXPOSING AGENTS

Examiner: R. P. Swartz

DECLARATION UNDER 37 C.F.R. § 1.132

Honorable Commissioner
OfPatents and Trademarks
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Prof. Dr. Jan Moilenhauer of the Department for Cancer and Inflammation, Institute for Molecular Medicine, University of Southern Denmark, Denmark, do hereby declare the following:

I have attached a copy of my curriculum vitae to this Declaration.
I am Professor for Molecular Oncology, Head of Molecular Oncology, and Director of The Lundbeck Foundation Nanomedicine Research Center for Cancer Stem Cell Targeting Therapeutics NanoCAN and have worked in the field of cancer and inflammation research for 16 years. I perform research on DMBT1 for 13 years now, and am one of the worlds leading experts in this field.
I am familiar with the above referenced patent application, as well as the in vitro and in vivo assays and development of treatments using DMBTI. I have read and understand the subject matter of the Office Action of January 25, 2010.

The following comments are offered in support of the patentability of the instant invention.

1. *In vivo* data in the specification supports that the presence of DMBT1 regulates inflammation through interaction of the DMBT1 protein with inflammatory agents.

DMBT1 knockout mice are more susceptible to intestinal inflammation than normal (wild type) mice. This is documented by data shown in figures 8-10 of the original application. The inflammation is caused by an agent corresponding to the specification in the claims, i.e. an agent carrying at least one accessible sulfate or phosphate group. Thus, the polypeptide prevents disease caused by such agents in terms of reducing the severity of symptoms. Because the effect is based on interaction with the specified agents and because this interaction is mediated by the claimed peptides, one of skill in the art can deduce from these data that the peptide would be applicable for disease prevention in an analogous manner.

2. The *in vivo* data in the specification is comparable to a therapeutic test.

The situation in the knockout mice (no DMBT1) versus wild type mice (DMBT1 present) is comparable to a therapeutic test, in which a placebo (no DMBT1) versus the polypeptide (DMBT1) is applied to an organism/patient. Presence of DMBT1 versus absence exerts a positive effect in mice in terms of reducing the severity of symptoms. Thus, the polypeptide can be considered to have a positive therapeutic effect on disease caused by the specified agents in terms of reducing the severity of symptoms. Because the effect is based on interaction with the specified agents and because this interaction is mediated by the claimed peptides, the skilled artisan can deduce from these data that the peptide would be applicable for achieving positive therapeutic effects in an analogous manner.

3. Further *in vivo* data supports that administration of DMBT1 as a protein would be effective as a therapeutic or preventative agent.

One of skill in the art would be able to determine the effectiveness of an application for

prevention and therapy of diseases caused by such agents from the description in the Specification. This effectiveness is confirmed by the new data shown in Table 1 below, which describes the association of DBMT1 polymorphisms with IBD.

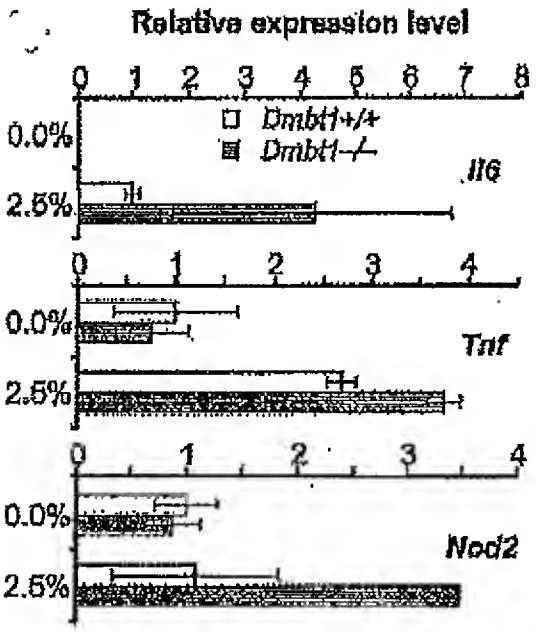
Table 1. Association of *DMBT1* Polymorphisms With IBD

	DMBT1[SNP]		*DMBT1*[SNP]		*DMBT1*[SR47]		*DMBT1*[SNP]	
	C:T (%)	CC:CT:TT (n)	T:C (%)	TT:CT:CC (n)	+:- (%)	++:+-:-- (n)	A:G (%)	AA:AG:GG (n)
Controls	71%:29%	138:112:25	74%:26%	128:92:16	86%:14%	192:69:2	52%:48%	68:120:86
IBD	72%:28%	326:278:45	75%:25%	306:211:36	81%:19%	845:187:5	52%:48%	176:280:151
		ns		ns		$P = .012$		ns
						1.49 (1.09–1.93)[a]		
CD	71%:29%	150:129:25	77%:23%	154:101:12	78%:22%	156:114:3	52%:48%	78:142:67
		ns		ns		$P = .00066$		ns
						1.75 (1.27–2.41)[a]		
UC	72%:28%	188:149:20	79%:27%	154:110:24	84%:16%	190:83:2	52%:48%	97:136:84
		ns		ns		ns		ns

ns, not significant.
[a]Odds ratio (95% confidence interval).

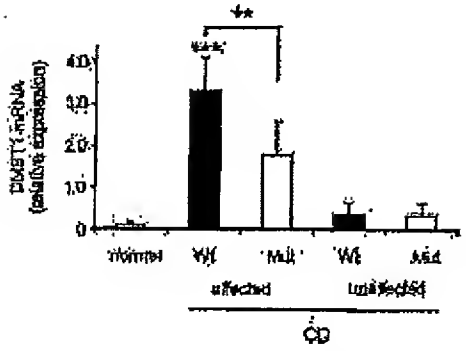
In the column *DMBT1*^{SR47} the frequency of the long variant ("+"; 13 of the agent-binding peptides) and the short variant (" "; only 8 of the agent-binding peptides) is compared in patients with chronic inflammatory disease of the intestine versus normal controls. A significant *over-representation* of the short variant is observed in patients with inflammatory bowel disease (IBD), in particular in patients with Crohn's disease (CD). An over-representation is also present - but not significant with the present case numbers – in patients with ulcerative colitis (UC). Thus, reduced function in capturing the specified agents results in increased disease risk, while increased function in capturing the specified agents results in reduced disease risk. Thus, the polypeptide and the peptides can be used for disease prevention and therapy.

4. One of skill in the art would be able to determine the effectiveness of an application for prevention and therapy of diseases caused by such agents from the description in the Specification. The figure below further demonstrates that an administration of DSS, an agent which causes inflammation, in DMBT1 positive mice showed decreased expression of agents associated with the inflammatory response when compared to the reaction in mice lacking DMBT1.



The data show that the presence of DMBT1 (in the DMBT1+/+ mice) inhibits activation of pro-inflammatory factors via the specified agents (in this case upon administration of 2.5% g/v DSS versus 0.0% g/v DSS) compared to the absence of DMBT1 (DMBT1-/- mice). Thus, an increase of the active polypeptide or agent-binding peptide amount in a patient, especially in such patients, which are diagnosed to have reduced amounts (see Table I above) can be applied to prevent the disease and to achieve positive therapeutic effects.

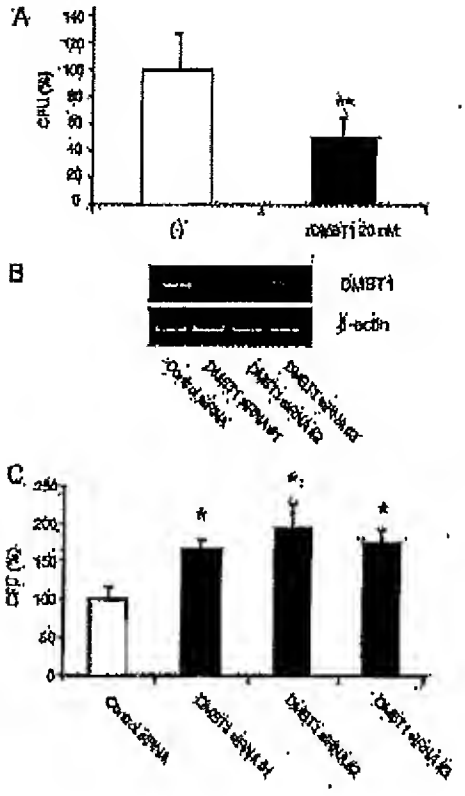
5. One of skill in the art would be able to determine the effectiveness of an application for prevention and therapy of diseases caused by such agents from the description in the Specification. This effectivenss is demonstrated by the new data shown in the figure below, which demonstrate that in patients with chronic inflammatory disease in the intestine DMBT1 is increased and that NOD2 mutation is tied to a decrease in DMBT1.



It shows that compared to healthy individuals (normal) a *moderate* upregulation of DMBT1 takes place in patients with chronic inflammatory disease in the intestine (CD patients), even though there is no visible inflammation (unaffected). A drastic upregulation takes place in the intestine of the patients upon outbreak of the inflammation (affected). The activation of DMBT1 is significantly *better* in patients with a normal variant (Wt) of the gene NOD2 compared to patients with a mutant variant (Mut) of NOD2. NOD2 mutations cause the disease.

Thus, disease-causing mutations in NOD2 result in lower total amounts of DMBT1, and accordingly reduce the absolute number of peptide binding sites for the agents specified in the invention. Thus a supplementation with either the polypeptide or the peptides of the invention would restore the active amount of binding sites for the specified agents and cause preventive or positive therapeutic effects (in conjunction with the data displayed above and with the data obtained from mice displayed in the original application). One of skill in the art would not require undue experimentation to obtain these effects using the data shown in the original invention.

6. One of skill in the art would be able to determine the effectiveness of an application for prevention and therapy of diseases caused by such agents from the description in the Specification. This effectiveness is confirmed by the new data shown in the figure below, which demonstrates that an *in vitro* administration of DMBT1 peptide to epithelial cells reduces bacterial infection.

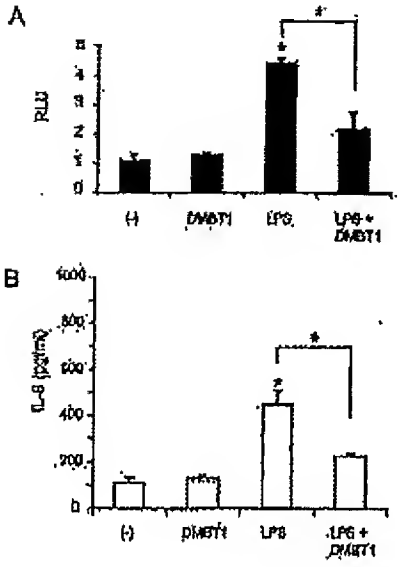


Panel A shows that addition of 20 nM human recombinant DMBT1 polypeptide (rDMBT1) significantly reduces bacterial infection of human epithelial cells. Panels B and C show that if DMBT1 is inactivated in human epithelial cells via siRNAs, this results in significantly increased bacterial infection. Thus the polypeptide can be used for prevention and therapy of disease caused by the specified agents. Because the interaction with the specified agents takes place via the peptide specified in the invention, these peptides can be used as substitutes.

7. Administration of the polypeptide of the invention reduces pro-inflammatory factors.

One of skill in the art would be able to determine the effectiveness of an application for prevention and therapy of diseases caused by such agents from the description in the

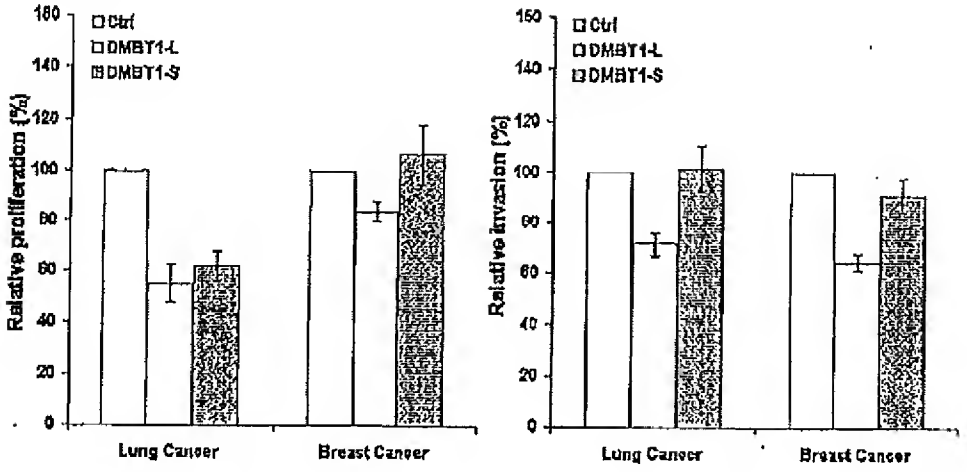
Specification. Such effectiveness is further confirmed by the new data shown in the figure below.



Panel A shows that the polypeptide of the invention (DMBT1) significantly reduces the pro-inflammatory activation of the factor NF-kB (measured in RLU) upon LPS. LPS is an agent according to the specification in the invention, which causes inflammation. Panel B shows that the polypeptide also significantly reduces the secretion of the pro-inflammatory cytokine IL-8. Thus, the polypeptide can be used for the prevention and therapy of inflammation. Because the *peptides* of the invention interact with the specified agents they can alternatively be used for prevention and therapy.

8. The number of inflammatory agent binding sequences is important to decrease resultant inflammation.

One of skill in the art would be able to determine the effectiveness of an application for prevention and therapy of diseases caused by such agents from the description in the Specification. This effectiveness is confirmed by the new data shown in the figure below.



The figure shows the effect of supplementation of the normal DMBT1 polypeptide (DMBT1-L) and of a DMBT1 polypeptide with a reduced number of agent-binding peptides (DMBT1-S) on cancer cells compared to controls (Ctrl) without supplementation. DMBT1-L reduces proliferation and invasion of cancer cells substantially better than DMBT1-S. Thus the polypeptide can be used for prevention and therapy of cancer caused by agents specified in the invention. Because the number of agent-binding peptide sequences is important for the positive effects, the skilled artisan would understand that the peptides of the invention could be used for prevention and therapy, without undue experimentation.

9. Since filing, other individuals of skill in the art have concluded that DMBT1 administration would be effective to prevent or treat a variety of diseases.

Other individuals of skill in the art have confirmed Applicants' finding that an application for prevention and therapy of *diseases* caused by such agents would be effective. Such confirmation can be found in the new data published in:

(1) Blackburn AC, et al. Genetic mapping in mice identifies DMBT1 as a candidate modifier of

mammary tumors and breast cancer risk. Am J Pathol 170:2030-2041 (2007). (attached)

(2) Tchatchou S, et al. Identification of a DMBT1 Polymorphism Associated with Increased Breast Cancer Risk and Decreased Promoter Activity. Hum Mut 31:60-66 (2010). (attached)

It is my opinion that one of skill in the art would have understood how to use the claimed method to effectively treat or prevent a variety of diseases without undue experimentation based on the disclosures of the Specification. As confirmation, the data presented above (from other skilled artisans, post-filing) show that mice and humans that display, via different mechanisms, a reduced number of agent-binding polypeptide/peptide sequences according to the invention have an increased risk for cancer. Accordingly, a supplementation with either the polypeptide or the peptides according to the invention can be applied for cancer prevention and therapy.

The undersigned hereby declares that all statements made herein based upon knowledge are true, and that all statements made based upon information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

DATED: 21.05.2010

Prof. Dr. Jan Mollenhauer

Attachments: Blackburn AC, et al.

Tchatchou S, et al.

CV PROF. DR. JAN MOLLENHAUER

1. BIOGRAPHIC DATA

Date of birth:	18.08.1968 (Kiel, Germany)
Nationality:	German

2. EDUCATION AND POSITIONS

June 1989	Certificate of business studies; Grade: "Sehr gut" (top mark)
1989 - 1994	Studies of Biology, University of Cologne, Germany
Sept. 1994	Diploma in Biology (equivalent to MSc)
1994 - 2008	Department Molecular Genome Analysis German Cancer Research Center (DKFZ), Heidelberg, Germany
June 1998:	Dr. rer. nat. (PhD), Faculty of Natural Sciences, University Heidelberg, Germany
June 1998 - June 2001	Postdoctoral assistant
April 2000	Course in International Business Management
June 2001 – Feb. 2008	Group leader
Nov. 2002 - Feb. 2008	Project manager, Dep. Molecular Genome Analysis (DKFZ)
Dec. 2003	State doctorate ("Habilitation") in Molecular Medicine, Faculty of Medicine, University Heidelberg, Germany Mentor: Prof. Harald zur Hausen (Nobel Laureate 2008)
Since March 2008	Full Professor for Molecular Oncology, Head of Molecular Oncology Institute for Molecular Medicine University of Southern Denmark, Odense
2008 - 2013	Head of two high-throughput drug screening projects within the German National Genome Research Network
2010 - 2014	Director Lundbeckfonden Center of Excellence NanoCAN

3. HONORS & AWARDS

June 1989	Award of the Chamber of Industry and Commerce: Recognition for outstanding performance in business studies
October 2003	Second award "Vincenz-Czerny award for Oncology 2003"
June 2005	Future Award for Health Sciences of the Helmholtz Association (200,000 €)
December 2005:	Acknowledgement from the German Cancer Research Center for outstanding contributions to science
January 2006:	Proposed for the Future Award of the German President
January 2007:	Listed in the "Who Is Who of Emerging Leaders" 2007
March 2009:	Award of the Leo og Ingeborg Dannins Fondens Legat (300,000 DKK)
April 2010:	Fyens Stiftstidende Forskerpris 2010 (15,000 DKK)

4. PUBLICATIONS

Scientific journals with impact factors (referred to the year of publication)
51 published original research papers

Average impact factor: 5.53 (6.98 for first and last author publications)
Citations of published articles (state: March 2009): 1087

1. Behn-Krappa A, Mollenhauer J, Doerfler W. Triplet repeat sequences in human DNA can be detected by hybridization to a synthetic (5`-CGG-3`)17 oligodeoxyribonucleotide. FEBS 333:248-250 (1993). IMPACT FACTOR: 3.504

2. Mollenhauer J, Wiemann S, Scheurlen W, Korn B, Hayashi Y, Wilgenbus KK, von Deimling A, Poustka A. DMBT1, a new member of the SRCR superfamily, on chromosome 10q25.3-q26.1 is deleted in malignant brain tumors. Nat Genet 17:32-39 (1997). IMPACT FACTOR: 38.854

3. Scheurlen WG, Schwabe GC, Joos S, Mollenhauer J, Sorensen N, Kuhl J. Molecular analysis of childhood primitive neuroectodermal tumors defines markers associated with poor outcome. J Clin Oncol 16:2478 2485 (1998). IMPACT FACTOR: 8.228

4. Mollenhauer J, Holmskov U, Wiemann S, Krebs I, Herbertz S, Madsen J, Kioschis P, Coy JF, Poustka A. The genomic structure of the DMBT1 gene: evidence for a region with susceptibility to genomic instability. Oncogene 18:6233-6240 (1999). IMPACT FACTOR: 6.517

5. Holmskov U, Mollenhauer J, Madsen J, Vitved L, Grönlund J, Tornoee I, Kliem A, Reid KBM, Poustka A, Skjoedt K. Cloning of gp-340, a putative opsonin receptor for lung surfactant protein D. Proc Natl Acad Sci USA 96:10794-10799 (1999). IMPACT FACTOR: 10.260

6. Hoff C, Seranski P, Mollenhauer J, Korn B, Detzel T, Reinhardt R, Ramser J, Poustka A. Physical and transcriptional mapping of the 17p13.3 region that is frequently deleted in human cancer. Genomics 70:26-33 (2000). IMPACT FACTOR: 3.425

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8. von Deimling A, Fimmers R, Schmidt MC, Bender B, Fassbender F, Nagel J, Jahnke R, Kaskel P, Duerr EM, Koopmann J, Maintz D, Steinbeck S, Wick W, Platten M, Müller DJ, Przkora R, Waha A, Blumcke B, Wellenreuther R, Meyer-Puttlitz B, Schmidt O, Mollenhauer J, Poustka A, Stangl AP, Lenartz D, von Ammon K. Comprehensive allelotype and genetic analysis of 466 human nervous system tumours. J Neuropathol Exp Neurol 59:544-558 (2000). IMPACT FACTOR: 5.565

9. Hoff C, Mollenhauer J, Waldau B, Hamann U, Poustka A. Allelic imbalance and fine mapping of the chromosome 17p13.3 subregion in sporadic breast carcinomas. Cancer Genet Cytogenet 129:145-149 (2001). IMPACT FACTOR: 1.529

10. Mollenhauer J, Herbertz S, Helmke B, Kollender G, Krebs I, Madsen J, Holmskov U, Sorger K, Schmitt L, Wiemann S, Otto HF, Gröne HJ, Poustka A. Deleted in Malignant Brain Tumors 1 is a versatile mucin-like molecule likely to play a differential role in digestive tract cancer. Cancer Res 61:8880-8886 (2001). IMPACT FACTOR: 8.302

11. Mollenhauer J, Helmke B, Müller H, Kollender G, Krebs I, Wiemann S, Holmskov U, Madsen J, Otto HF, Poustka A. An integrative model on the role of DMBT1 in epithelial cancer. Cancer Detect Prevent 26:266-274 (2002). IMPACT FACTOR: 1.289

12. Deichmann M*, Mollenhauer J*, Helmke B, Thome M, Hartschuh W, Poustka A, Näher H. Analysis of losses of heterozygosity of the candidate tumor suppressor gene DMBT1 in uncultured malignant melanomas. Oncology 63:166-172 (2002). *Shared first authorship. IMPACT FACTOR: 2.330

13. Mollenhauer J, Helmke B, Müller H, Kollender G, Lyer S, Diedrichs L, Holmskov U, Ligtenberg T, Herbertz S, Krebs I, Wiemann S, Madsen J, Bikker F, Schmitt L, Otto HF, Poustka A. Sequential changes of the DMBT1 expression and location in normal lung tissue and lung carcinomas. Genes Chrom Cancer 35:164-169 (2002). IMPACT FACTOR: 4.199

14. Mollenhauer J, Müller H, Kollender G, Lyer S, Diedrichs L, Helmke B, Holmskov U, Ligtenberg T, Herbertz S, Krebs I, Madsen J, Bikker F, Schmitt L, Wiemann S, Scheurlen W, Otto HF, von Deimling A, Poustka A. The SRCR/SID region of DMBT1 defines a complex multi-allele system representing the major basis for its variability in cancer. Genes Chrom Cancer 35:242-255 (2002). IMPACT FACTOR: 4.199

15. Mueller W, Mollenhauer J, Stockhammer F, Poustka A, von Deimling A. Rare mutations of the DMBT1 gene in astrocytic gliomas. Oncogene 21:5956-5959 (2002). IMPACT FACTOR: 5.979

16. Wittig R, Nessling M, Will R, Mollenhauer J, Salowsky R, Münstermann E, Schick M, Helmbach H, Geschwendt B, Korn B, Kioschis P, Lichter P, Schadendorf D, Poustka A. Candidate genes for cross resistance against DNA-damaging drugs. Cancer Res 62:6698-6705 (2002). IMPACT FACTOR: 8.318

17. Bikker FJ, Ligtenberg AJM, Nazmi K, Veerman ECI, van`t Hof W, Bolscher JGM, Poustka A, Nieuw Amerongen AV, Mollenhauer J. Identification of the bacteria-binding peptide domain on salivary agglutinin (gp-340/DMBT1), a member of the scavenger receptor cysteine-rich superfamily. J Biol Chem 277:32109-32115 (2002) IMPACT FACTOR: 6.696

18. Mollenhauer J, Deichmann M, Helmke B, Müller H, Kollender G, Holmskov U, Ligtenberg T, Krebs I, Wiemann S, Bantel-Schaal U, Madsen J, Bikker F, Klauck SM, Otto HF, Moldenhauer G,

Poustka A. Frequent downregulation of DMBT1 and Galectin-3 in epithelial skin cancer. Int J Cancer 105:149-157 (2003). IMPACT FACTOR: 4.375

19. Sasaki M, Huang SF, Chen MF, Jan YY, Yeh TS, Ishikawa A, Mollenhauer J, Poustka A, Tsuneyama K, Nimura Y, Oda K, Nakanuma Y. Expression of Deleted in Malignant Brain Tumours 1 (DMBT1) molecule in biliary epithelium is augmented in hepatolithiasis: possible participation in lithogenesis. Digest Dis Sci 48:1234-1240 (2003). IMPACT FACTOR: 1.387

20. Sasaki M, Huang SF, Chen MF, Jan YY, Yeh TS, Ishikawa A, Mollenhauer J, Poustka A, Tsuneyama K, Nimura Y, Oda K, Nakanuma Y. Decrease of Deleted in Malignant Brain Tumours 1 (DMBT1) expression is a crucial late event in intrahepatic cholangiocarcinoma. Histopathology 43:340-346 (2003). IMPACT FACTOR: 2.952

21. Madsen J, Tornoe I, Nielsen O, Krebs I, Mollenhauer J, Poustka A, Skjoedt K, Holmskov U. CRP-ductin, the mouse homologue of gp-340/DMBT1 binds specifically to lung surfactant protein D (SP-D). Eur J Immunol 33:2327-2336 (2003). IMPACT FACTOR: 4.536

22. Sasaki M, Tsuneyama K, Saito T, Kataoka H, Mollenhauer J, Poustka A, Nakanuma Y. Site-characteristic expression and induction of trefoil factor family 1, 2 and 3 and Deleted in malignant brain tumors 1 in normal and diseased intrahepatic bile ducts relates to biliary pathophysiology. Liver Int 24:29-37 (2004). IMPACT FACTOR: 1.227

23. Mollenhauer J*, Helmke B*, Medina D, Kollender G, Müller H, Lyer S, Diedrichs L, Renner M, Wittig R, Blaich S, Madsen J, Holmskov U, Bikker F, Ligtenberg T, Carlen A, Olsson J, Otto HF, O'Malley B, Poustka A. Carcinogen-Inducibility in vivo and frequent down-regulation of DMBT1 during breast carcinogenesis. Genes Chrom Cancer 39:185-194 (2004). *Shared first authorship. IMPACT FACTOR: 4.276

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31. End C, Lyer S, Renner M, Stahl C, Ditzer J, Holloschi A, Kuhn HM, Flammann HT, Poustka A, Hafner M, Mollenhauer J*, Kioschis P*. Generation of a vector system facilitating cloning of DMBT1 variants and recombinant expression of functional full-length DMBT1. Protein Expr Purif 41:275-286 (2005). *Shared last authorship. IMPACT FACTOR: 1.553

32. Hartwin P, Hardern I, Wittig R, Mollenhauer J, Poustka A, Salowsky R, Wulff T, Rizzo C, Wilson B. Utility of lab-on-a-chip technology of high-throughput nucleic acid and protein analysis. Electrophoresis 26:3674-3681 (2005). IMPACT FACTOR: 3.850

33. Robbe C, Paraskeva C, Mollenhauer J, Michalski JC, Sergi C, Corfield A. DMBT1 expression and glycosylation during the adenoma-carcinoma sequence in colorectal cancer. Biochem Soc Trans 33:730-732 (2005). IMPACT FACTOR: 3.099

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35. Haase B, Humphray SJ, Lyer S, Renner M, Poustka A, Mollenhauer J, Leeb T. Molecular characterization of the porcine deleted in malignant brain tumors 1 gene (DMBT1). Gene 376:184-191 (2006). IMPACT FACTOR: 2.721

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